

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>JPD/GJW/KB123PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 99/ 02157</b>	International filing date (day/month/year) <b>06/07/1999</b>	(Earliest) Priority Date (day/month/year) <b>06/07/1998</b>
Applicant <b>KARO BIO AB et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 9 sheets.



It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.



the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☒ **Unity of invention is lacking** (see Box II).

**4. With regard to the title,**

the text is approved as submitted by the applicant.



the text has been established by this Authority to read as follows:

**5. With regard to the abstract,**

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

**6. The figure of the drawings to be published with the abstract is Figure No.**

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/GB 99/02157

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 9-19, 20 (partially) and 21-26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
  
Present claims
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.2

Present claims 1-19,21-29 relate to a compounds defined (inter alia) by reference to the following parameter(s):

P1: ERbeta ligand, agonist, antagonist.

P2: ERalpha ligand, agonist, antagonist.

The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the compounds specifically mentioned in claim 20, i.e. genistein.

The term chemical derivative or structural analogue of genistein is not clear in the present context because it is not possible for the skilled man in the field of therapeutics to exhaustively list the compounds which are comprised within the scope of claim 20.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

**1. Claims: 1-26**

A composition comprising an Estrogen Receptor beta ligand and its use as vasculoprotective.

**2. Claims: 27-29**

A method for producing artificial tissues or organs including the step of treating the tissue with an ERbeta agonist and artificial tissues and organs obtained by such method.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02157

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/35 C12N5/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C12N A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EMBASE, BIOSIS, MEDLINE, EPO-Internal, PAJ, WPI Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LINDNER, VOLKHARD ET AL: "Increased expression of estrogen receptor - . beta. mRNA in male blood vessels after vascular injury" CIRC. RES. (1998), 83(2), 224-229, XP000856530 abstract page 227, column 1 -page 228, column 1 --- -/--	1-19, 21-26

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

28 June 2000

Date of mailing of the international search report

11. 07. 2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Ryckebosch, A

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02157

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WILLIAMS J.K. ET AL: "Estrogens, progestins, and coronary artery reactivity in atherosclerotic monkeys." JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, (1998) 65/1-6 (219-224)., XP002126532 abstract page 223, column 1, paragraph 2 -page 223, column 2, paragraph 3 ----</p>	1-26
X	<p>TAKAMURA, HIROYUKI: "Immunosuppressive effects of a tyrosine kinase specific inhibitors ( genistein ) on the rejection of rat allogeneic small bowel transplantation" KANAZAWA DAIGAKU JUZEN IGAKKAI ZASSHI (1995), 104(6), 719-731, XP002126533 abstract; figure 2; tables 2,3 ----</p>	10-12
X	<p>BECKELER, KLAUS ET AL: "Differential effects of immunosuppressive cyclosporine A and inhibitors of protein kinases on cytokine induced cell proliferation of umbilical cord artery smooth muscle cells: The role of endothelial supernatants on TNF-alpha effects." EUROPEAN JOURNAL OF CELL BIOLOGY, (1996) VOL. 69, NO. SUPPL. 42, PP. 126. MEETING INFO.: 21ST ANNUAL MEETING OF THE GERMAN SOCIETY FOR CELL BIOLOGY HAMBURG, GERMANY MARCH 24-28, 1996, XP002126534 abstract ----</p>	10-12
X	<p>TROVATI M. ET AL: "Insulin increases cyclic nucleotide content in human vascular smooth muscle cells: A mechanism potentially involved in insulin-induced modulation of vascular tone." DIABETOLOGIA, (1995) 38/8 (936-941)., XP002126535 abstract page 936, column 1, paragraphs 1,2 ----</p>	1-20, 22-26
A	<p>KUIPER ET AL.: "Comparison of the ligand Binding Specificity and Transcript Distribution of Estrogen Receptors alpha and beta" ENDOCRINOLOGY, vol. 138, no. 3, 1997, pages 863-870, XP002126536 cited in the application abstract; table 1 ----</p>	1-26
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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02157

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KAPIOTIS S ET AL: "Genistein, the dietary-derived angiogenesis inhibitor, prevents LDL oxidation and protects endothelial cells from damage by atherogenic LDL." ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1997 NOV) 17 (11) 2868-74., XP002126537 abstract ---	1-26
X	BALARAM S.K. ET AL: "Cell adhesion molecules and insulin-like growth factor-1 in vascular disease." JOURNAL OF VASCULAR SURGERY, (1997) 25/5 (866-876)., XP002126538 abstract ---	1-26
X	HONORE E K ET AL: "Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques." FERTILITY AND STERILITY, (1997 JAN) 67 (1) 148-54., XP002126539 abstract page 148, column 1, paragraph 1 -page 152, column 1, paragraph 1 ---	1-26
X	CLARKSON T.B. ET AL: "The nonhuman primate model of the relationship between gonadal steroids and coronary heart disease." PROGRESS IN CARDIOVASCULAR DISEASES, (1995) 38/3 (189-198)., XP002126540 page 197, column 1, paragraph 2 -column 2, paragraph 2 ---	1-26
E	US 5 919 813 A (DE JUAN JR EUGENE) 6 July 1999 (1999-07-06) abstract ---	1-26
X	DATABASE WPI Section Ch, Week 199826 Derwent Publications Ltd., London, GB; Class B02, AN 1998-292041 XP002126542 & JP 10 101561 A (SHIKOKU NOGYO SHIKENJO), 21 April 1998 (1998-04-21) abstract --- -/--	1-22

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02157

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE WPI  Section Ch, Week 199720  Derwent Publications Ltd., London, GB;  Class A96, AN 1997-215838  XP002126543  &amp; JP 09 056807 A (KANEBUCHI KAGAKU KOGYO KK), 4 March 1997 (1997-03-04)</p>	1-26
Y	<p>abstract</p>	27-29
Y	<p>WO 93 23090 A (SHERWOOD MEDICAL COMPANY)  25 November 1993 (1993-11-25)  page 6, line 7 - line 12; claims</p>	27-29
P, X	<p>DATABASE WPI  Section Ch, Week 199932  Derwent Publications Ltd., London, GB;  Class B02, AN 1999-374524  XP002126544  &amp; JP 11 139974 A (KUREHA CHEM IND CO LTD),  25 May 1999 (1999-05-25)  abstract</p>	1-26
X	<p>M S ANTHONY ET AL: "Soybean isoflavones  improve cardiovascular risk factors  without affecting the reproductive system  of peripubertal rhesus monkeys"  JOURNAL OF NUTRITION, XX, XX,  vol. 126, no. 1, page 43-50 XP002095625  ISSN: 0022-3166  abstract</p>	1-26
X	<p>WO 98 08503 A (NOVOGEN RES PTY LTD)  5 March 1998 (1998-03-05)  abstract  page 3, line 3  page 6, line 7 -page 7, line 24</p>	1-26
P, X	<p>ST CLAIR R.W.: "Estrogens and  atherosclerosis: Phytoestrogens and  selective estrogen receptor modulators."  CURRENT OPINION IN LIPIDOLOGY, (1998) 9/5  (457-463).,  XP002126541  the whole document</p>	1-26
A	<p>WO 97 09348 A (KAROBIO AB ;KUIPER GEORGE G  J M (SE); ENMARK EVA (SE); GUSTAFSSON)  13 March 1997 (1997-03-13)  the whole document</p>	1-26



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02157

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5919813 A	06-07-1999	AU 3001999 A WO 9945920 A	27-09-1999 16-09-1999
JP 10101561 A	21-04-1998	JP 2829388 B	25-11-1998
JP 9056807 A	04-03-1997	NONE	
WO 9323090 A	25-11-1993	JP 5317408 A AU 4252993 A	03-12-1993 13-12-1993
JP 11139974 A	25-05-1999	NONE	
WO 9808503 A	05-03-1998	AU 4003497 A BR 9713180 A CN 1233173 A EP 0954302 A GB 2331015 A NO 990965 A	19-03-1998 18-01-2000 27-10-1999 10-11-1999 12-05-1999 26-02-1999
WO 9709348 A	13-03-1997	AT 183516 T AU 715528 B AU 6988096 A CA 2201098 A DE 69603827 D DE 69603827 T DE 792292 T EP 0792292 A EP 0935000 A ES 2135249 T GR 98300029 T GR 3031618 T JP 11502417 T US 5958710 A	15-09-1999 03-02-2000 27-03-1997 13-03-1997 23-09-1999 24-02-2000 03-09-1998 03-09-1997 11-08-1999 16-10-1999 30-04-1998 31-01-2000 02-03-1999 28-09-1999

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents  
United States Patent and Trademark  
Office  
Box PCT  
Washington, D.C.20231  
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

<b>Date of mailing (day/month/year)</b> 10 March 2000 (10.03.00)	
<b>International application No.</b> PCT/GB99/02157	<b>Applicant's or agent's file reference</b> JPD/GJW/KB123PCT
<b>International filing date (day/month/year)</b> 06 July 1999 (06.07.99)	<b>Priority date (day/month/year)</b> 06 July 1998 (06.07.98)
<b>Applicant</b> HAYRY, Pekka et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

03 February 2000 (03.02.00)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

<p>The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland</p> <p>Facsimile No.: (41-22) 740.14.35</p>	<p>Authorized officer</p> <p>S. Mafra</p> <p>Telephone No.: (41-22) 338.83.38</p>
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## P. . . ENT COOPERATION TREA . .

PCT

NOTIFICATION OF THE RECORDING  
OF A CHANGE(PCT Rule 92bis.1 and  
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

DEAN, John, Paul  
Withers & Rogers  
Goldings House  
2 Hays Lane  
London SE1 2HW  
ROYAUME-UNIDate of mailing (day/month/year)  
01 March 2000 (01.03.00)Applicant's or agent's file reference  
JPD/GJW/KB123PCTInternational application No.  
PCT/GB99/02157

## IMPORTANT NOTIFICATION

International filing date (day/month/year)  
06 July 1999 (06.07.99)

## 1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

## Name and Address

DEAN, John, Paul  
Withers & Rogers  
Goldings House  
2 Hays Lane  
London SE1 2HW  
United KingdomState of Nationality  
GBState of Residence  
GB

Telephone No.

Facsimile No.

Teleprinter No.

## 2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

## Name and Address

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

## 3. Further observations, if necessary:

the applicant has been deleted from the record.

## 4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned  
☒ the International Searching Authority ☐ the elected Offices concerned  
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

F. Gateau

Telephone No.: (41-22) 338.83.38

PCT

## REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

COPY

For receiving Office use only

09/719658

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference  
(if desired) (12 characters maximum)

JPD/GJW/KB123PCT

## Box No. I TITLE OF INVENTION

VASCULOPROTECTOR

## Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KARO BIO AB  
NOVUM  
S-141 57 HUDDINGE  
SWEDEN

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant  
for the purposes of:☐all designated  
States☒all designated States except  
the United States of America☐the United States  
of America only☐the States indicated in  
the Supplemental Box

## Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DEAN, JOHN PAUL  
C/O WITHERS & ROGERS  
GOLDINGS HOUSE  
2 HAYS LANE  
LONDON SE1 2HW

This person is:

☒ applicant only☐ applicant and inventor☐ inventor only (If this check-box  
is marked, do not fill in below.)

State (that is, country) of nationality:

GB

State (that is, country) of residence:

GB

This person is applicant  
for the purposes of:☐all designated  
States☒all designated States except  
the United States of America☐the United States  
of America only☐the States indicated in  
the Supplemental Box☐ Further applicants and/or (further) inventors are indicated on a continuation sheet.

## Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf  
of the applicant(s) before the competent International Authorities as:

☒

agent

☐

common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

DEAN, John Paul  
WITHERS & ROGERS  
Goldings House  
2, Hays Lane  
LONDON SE1 2HW

Telephone No.

+44 117 925 3030

Facsimile No.

+44 117 925 3530

Teleprinter No.

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)**

*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

HAYRY, Professor Pekka  
Professor of Transplantation Surgery and Immunology  
Transplantation Laboratory  
P.O Box 21 (Haartmaninkatu 3)  
FIN 00014 University of Helsinki  
FINLAND

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
FI

State (that is, country) of residence:  
FI

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MAKELA, Sari  
Turun Yliopisto  
Biolaaketiede  
Anatomia  
Kiinanmyllynkaty 10 20520  
FINLAND

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
FI

State (that is, country) of residence:  
FI

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

GUSTAFSSON, Professor Jan-Ake  
c/o Karolinski Institute  
Novum  
S-151 57 Huddinge  
SWEDEN

This person is:

- ☐ applicant only  
☒ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:  
SE

State (that is, country) of residence:  
SE

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only  
☐ applicant and inventor  
☐ inventor only (If this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

**B x No.V DESIGNATION OF STATES**

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

**Regional Patent**

- ☐ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, SD Sudan, SZ Swaziland, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line) .....

**National Patent (if other kind of protection or treatment desired, specify on dotted line):**

- |   |   |
|---|---|
| <input type="checkbox"/> AL Albania .....                               | <input type="checkbox"/> LS Lesotho .....                                   |
| <input type="checkbox"/> AM Armenia .....                               | <input type="checkbox"/> LT Lithuania .....                                 |
| <input type="checkbox"/> AT Austria .....                               | <input type="checkbox"/> LU Luxembourg .....                                |
| <input checked="" type="checkbox"/> AU Australia .....                  | <input type="checkbox"/> LV Latvia .....                                    |
| <input type="checkbox"/> AZ Azerbaijan .....                            | <input type="checkbox"/> MD Republic of Moldova .....                       |
| <input type="checkbox"/> BA Bosnia and Herzegovina .....                | <input type="checkbox"/> MG Madagascar .....                                |
| <input type="checkbox"/> BB Barbados .....                              | <input type="checkbox"/> MK The former Yugoslav Republic of Macedonia ..... |
| <input type="checkbox"/> BG Bulgaria .....                              | <input type="checkbox"/> MN Mongolia .....                                  |
| <input type="checkbox"/> BR Brazil .....                                | <input type="checkbox"/> MW Malawi .....                                    |
| <input type="checkbox"/> BY Belarus .....                               | <input type="checkbox"/> MX Mexico .....                                    |
| <input checked="" type="checkbox"/> CA Canada .....                     | <input type="checkbox"/> NO Norway .....                                    |
| <input type="checkbox"/> CH and LI Switzerland and Liechtenstein .....  | <input checked="" type="checkbox"/> NZ New Zealand .....                    |
| <input type="checkbox"/> CN China .....                                 | <input type="checkbox"/> PL Poland .....                                    |
| <input type="checkbox"/> CU Cuba .....                                  | <input type="checkbox"/> PT Portugal .....                                  |
| <input type="checkbox"/> CZ Czech Republic .....                        | <input type="checkbox"/> RO Romania .....                                   |
| <input type="checkbox"/> DE Germany .....                               | <input type="checkbox"/> RU Russian Federation .....                        |
| <input type="checkbox"/> DK Denmark .....                               | <input type="checkbox"/> SD Sudan .....                                     |
| <input type="checkbox"/> EE Estonia .....                               | <input type="checkbox"/> SE Sweden .....                                    |
| <input type="checkbox"/> ES Spain .....                                 | <input type="checkbox"/> SG Singapore .....                                 |
| <input type="checkbox"/> FI Finland .....                               | <input type="checkbox"/> SI Slovenia .....                                  |
| <input type="checkbox"/> GB United Kingdom .....                        | <input type="checkbox"/> SK Slovakia .....                                  |
| <input type="checkbox"/> GD Grenada .....                               | <input type="checkbox"/> SL Sierra Leone .....                              |
| <input type="checkbox"/> GE Georgia .....                               | <input type="checkbox"/> TJ Tajikistan .....                                |
| <input type="checkbox"/> GH Ghana .....                                 | <input type="checkbox"/> TM Turkmenistan .....                              |
| <input type="checkbox"/> GM Gambia .....                                | <input type="checkbox"/> TR Turkey .....                                    |
| <input type="checkbox"/> HR Croatia .....                               | <input type="checkbox"/> TT Trinidad and Tobago .....                       |
| <input type="checkbox"/> HU Hungary .....                               | <input type="checkbox"/> UA Ukraine .....                                   |
| <input type="checkbox"/> ID Indonesia .....                             | <input type="checkbox"/> UG Uganda .....                                    |
| <input type="checkbox"/> IL Israel .....                                | <input checked="" type="checkbox"/> US United States of America .....       |
| <input type="checkbox"/> IN India .....                                 | <input type="checkbox"/> UZ Uzbekistan .....                                |
| <input type="checkbox"/> IS Iceland .....                               | <input type="checkbox"/> VN Viet Nam .....                                  |
| <input checked="" type="checkbox"/> JP Japan .....                      | <input type="checkbox"/> YU Yugoslavia .....                                |
| <input type="checkbox"/> KE Kenya .....                                 | <input type="checkbox"/> ZW Zimbabwe .....                                  |
| <input type="checkbox"/> KG Kyrgyzstan .....                            |   |
| <input type="checkbox"/> KP Democratic People's Republic of Korea ..... |   |
| <input checked="" type="checkbox"/> KR Republic of Korea .....          |   |
| <input type="checkbox"/> KZ Kazakhstan .....                            |   |
| <input type="checkbox"/> LC Saint Lucia .....                           |   |
| <input type="checkbox"/> LK Sri Lanka .....                             |   |
| <input type="checkbox"/> LR Liberia .....                               |   |

Check-boxes reserved for designating States (for the purposes of a national patent) which have become party to the PCT after issuance of this sheet:

- ☐ .....
- ☐ .....
- ☐ .....

**Precautionary Designation Statement:** In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation of a designation consists of the filing of a notice specifying that designation and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.)

**ADDITIONAL REPRESENTATIVES**

**PATENT CO-OPERATION TREATY**

D. G. Bannerman  
N. M. Wilson  
W. M. Blatchford  
M. Adkins  
A. J. Chettle  
J. K. Hogg  
J. P. Dean

I. S. Harrison  
D. M. Pratt  
B. J. N. Dempster  
K. J. Barnfather  
S. A. Beck  
P. C. Turner  
H. H. B. Wright

D. Croston  
D. C. Jones

of:

**WITHERS & ROGERS**  
**Goldings House**  
**2 Hays Lane**  
**London SE1 2HW**  
**UNITED KINGDOM**

<b>B x No. VI PRIORITY CLAIM</b>					<input type="checkbox"/> Further priority claims are indicated in the Supplemental Box.
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:			
		national application: country	regional application:* regional Office	international application: receiving Office	
item (1) 06/07/98	9814620.2	GB			
item (2)					
item (3)					

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (1)

\* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.

<b>B x No. VII INTERNATIONAL SEARCHING AUTHORITY</b>			
<b>Choice of International Searching Authority (ISA)</b> (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):		<b>Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):</b>	
ISA /		Date (day/month/year)	Number Country (or regional Office)

<b>Box No. VIII CHECK LIST; LANGUAGE OF FILING</b>	
This international application contains the following number of sheets: request : 5 description (excluding sequence listing part) : 16 claims : 3 abstract : 1 drawings : 5 sequence listing part of description : <b>T tal number of sheets : 30</b>	This international application is accompanied by the item(s) marked below: 1. <input type="checkbox"/> fee calculation sheet 2. <input type="checkbox"/> separate signed power of attorney 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: 4. <input type="checkbox"/> statement explaining lack of signature 5. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): 6. <input type="checkbox"/> translation of international application into (language): 7. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material 8. <input type="checkbox"/> nucleotide and/or amino acid sequence listing in computer readable form 9. <input type="checkbox"/> other (specify):
Figure of the drawings which should accompany the abstract:	Language of filing of the international application:

<b>B x No. IX SIGNATURE OF APPLICANT OR AGENT</b>	
Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).	
..... <u>DEAN</u> , John Paul - Withers & Rogers	

For receiving Office use only	
1. Date of actual receipt of the purported international application: 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: 4. Date of timely receipt of the required corrections under PCT Article 11(2): 5. International Searching Authority (if two or more are competent): ISA /	2. Drawings: <input type="checkbox"/> received: <input type="checkbox"/> not received: 6. <input type="checkbox"/> Transmittal of search copy delayed until search fee is paid.

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	



COPY

**Request for a certificate of the  
Comptroller or a certified or uncertified  
copy from a file or the register**

*(See the notes on the back of this form)*

The Patent Office

Cardiff Road  
Newport  
Gwent NP9 1RH

- 
1. Your reference JPD/GJW/KLB/KB123PCT
- 
2. Patent application or patent number(s)  
*(see notes (c) & (d))* GB9814620.2
- 
3. Full name of the or of each patent applicant or  
proprietor KARO BIO AB  
*(if known)*
- 
4. What do you want a copy of? *(see note (f))* APPLICATION AS FILED
- 
5. How many copies do you need? ONE
- 
6. State the type of certificate you want  
*(see note (g))* and if it is needed to support  
applications made outside the United  
Kingdom, list the countries concerned  
*(see notes (j) & (k))* PLEASE TRANSFER CERTIFIED COPY OF GB9814620.2  
TO THE FILE OF THE NEW INTERNATIONAL APPLICATION  
FILED HERewith TO ACT AS A PRIORITY DOCUMENT.
- 
7. Name, address and postcode of the or of each  
person making this request  
*(see note (h))* WITHERS & ROGERS  
GOLDINGS HOUSE  
2 HAYS LANE  
LONDON  
SE1 2HW
- 
8. Name, address and postcode of the or of each  
person certificates or copies should be sent to  
*(if different from that given in part 6 above)*  
*(see note (i))*

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

DEAN, John P.  
WITHERS & ROGERS  
Goldings House  
2 Hays Lane  
London SE1 2HW  
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT  
(PCT Rule 71.1)

Date of mailing  
(day/month/year) 02.11.2000

Applicant's or agent's file reference  
KB123PCT

IMPORTANT NOTIFICATION

International application No.  
PCT/GB99/02157

International filing date (day/month/year)  
06/07/1999

Priority date (day/month/year)  
06/07/1998

Applicant  
KARO BIO AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Emslander, S

Tel. +49 89 2399-8718



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference <b>KB123PCT</b>	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. <b>PCT/GB99/02157</b>	International filing date (day/month/year) <b>06/07/1999</b>	Priority date (day/month/year) <b>06/07/1998</b>
International Patent Classification (IPC) or national classification and IPC <b>C07K14/00</b>		
Applicant <b>KARO BIO AB et al.</b>		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 9 sheets, including this cover sheet.
  - ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☒ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand <b>03/02/2000</b>	Date of completion of this report <b>02.11.2000</b>
Name and mailing address of the international preliminary examining authority:  <b>European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</b>	Authorized officer <b>Heimann-Pohl, B</b>  Telephone No. +49 89 2399 8713 

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02157

## I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

### Description, pages:

1-16 as originally filed

### Claims, No.:

1-29 as originally filed

### Drawings, sheets:

1/5-5/5 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

## II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB99/02157

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-2 (partially), 4-29 (partially), 3.

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1,2,4-19, 20 (partially), 21-29 (partially), 3.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/02157

- ☐ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
- ☒ not complied with for the following reasons:
- see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☒ all parts.
- ☐ the parts relating to claims Nos. .

## V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

### 1. Statement

Novelty (N)	Yes:	Claims 27, 28
	No:	Claims 1, 2, 4-26, 29
Inventive step (IS)	Yes:	Claims
	No:	Claims 27-29
Industrial applicability (IA)	Yes:	Claims 1,2,4-8, 27-29; 20 (partially)
	No:	Claims

### 2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/02157

1). Non-unity (Box IV)

The International Preliminary Examination Authority (IPEA) agrees with the finding of the International Searching Authority (ISA) that the international application contains 2 inventions.

The problems to be solved by the present application are (1) to provide for a vasculoprotective composition and to provide for vasculoprotection and (2) to provide a method for producing artificial tissues or organs and artificial tissues or organs obtained by said method.

The proposed solution for (1) is to use ER $\beta$  ligands, e.g. genistein, as vasculoprotector and the proposed solution for (2) is to treat a tissue with an agonist of ER $\beta$  and thereby obtaining artificial tissues or organs.

The additional fee was paid, hence examination will be carried out for invention 1 and 2.

2). No Search (Box III)

The unspecified antagonist of claim 3, the unspecified ligands and agonists of claims 1, 2, 4-19 and 21-29 (or the uses of these substances) and the chemical derivative or structural analogue of claim 20 were not searched since the lack of clarity was such that a meaningful complete search was impossible.

Consequently, it is not possible to carry out a preliminary examination on matter which has not been searched.

Search was restricted to genistein, thus all claims are examined with regard to genistein.

3). Prior art

D1: LINDNER, VOLKHARD ET AL: 'Increased expression of estrogen receptor - beta. mRNA in male blood vessels after vascular injury' CIRC. RES. (1998), 83(2), 224-229, XP000856530

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/02157

- D2: WILLIAMS J.K. ET AL: 'Estrogens, progestins, and coronary artery reactivity in atherosclerotic monkeys.' JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, (1998) 65/1-6 (219-224)., XP002126532
- D3: TAKAMURA, HIROYUKI: 'Immunosuppressive effects of a tyrosine kinase specific inhibitors ( genistein ) on the rejection of rat allogeneic small bowel transplantation' KANAZAWA DAIGAKU JUZEN IGAKKAI ZASSHI (1995), 104(6), 719-731, XP002126533
- D4: BECKELER, KLAUS ET AL: 'Differential effects of immunosuppressive cyclosporine A and inhibitors of protein kinases on cytokine induced cell proliferation of umbilical cord artery smooth muscle cells: The role of endothelial supernatants on TNF-alpha effects.' EUROPEAN JOURNAL OF CELL BIOLOGY, (1996) VOL. 69, NO. SUPPL. 42, PP. 126. MEETING INFO.: 21ST ANNUAL MEETING OF THE GERMAN SOCIETY FOR CELL BIOLOGY HAMBURG, GERMANY MARCH 24-28, 1996, XP002126534
- D5: KUIPER ET AL.: 'Comparison of the ligand Binding Specificity and Transcript Distribution of Estrogen Receptors alpha and beta' ENDOCRINOLOGY, vol. 138, no. 3, 1997, pages 863-870, XP002126536 cited in the application
- D6: KAPIOTIS S ET AL: 'Genistein, the dietary-derived angiogenesis inhibitor, prevents LDL oxidation and protects endothelial cells from damage by atherogenic LDL.' ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1997 NOV) 17 (11) 2868-74., XP002126537
- D7: BALARAM S.K. ET AL: 'Cell adhesion molecules and insulin-like growth factor-1 in vascular disease.' JOURNAL OF VASCULAR SURGERY, (1997) 25/5 (866-876)., XP002126538
- D8: HONORE E K ET AL: 'Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques.' FERTILITY AND STERILITY, (1997 JAN) 67 (1) 148-54., XP002126539
- D9: CLARKSON T.B. ET AL: 'The nonhuman primate model of the relationship between gonadal steroids and coronary heart disease.' PROGRESS IN CARDIOVASCULAR DISEASES, (1995) 38/3 (189-198)., XP002126540
- D10: US-A-5 919 813 (DE JUAN JR EUGENE) 6 July 1999 (1999-07-06)
- D11: DATABASE WPI Section Ch, Week 199826 Derwent Publications Ltd., London, GB; Class B02, AN 1998-292041 XP002126542 & JP 10 101561 A (SHIKOKU NOGYO SHIKENJO), 21 April 1998 (1998-04-21)
- D12: DATABASE WPI Section Ch, Week 199720 Derwent Publications Ltd.,



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB99/02157

London, GB; Class A96, AN 1997-215838 XP002126543 & JP 09 056807 A  
(KANEBUCHI KAGAKU KOGYO KK), 4 March 1997 (1997-03-04)

D13: M S ANTHONY ET AL: 'Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys' JOURNAL OF NUTRITION, XX, XX, vol. 126, no. 1, page 43-50  
XP002095625 ISSN: 0022-3166

D14: WO 98 08503 A (NOVOGEN RES PTY LTD) 5 March 1998 (1998-03-05)

D15: WO 93 23090 A (SHERWOOD MEDICAL COMPANY) 25 November 1993  
(1993-11-25)

D16: DATABASE WPI Section Ch, Week 199932 Derwent Publications Ltd.,  
London, GB; Class B02, AN 1999-374524 XP002126544 & JP 11 139974 A  
(KUREHA CHEM IND CO LTD), 25 May 1999 (1999-05-25)

D17: ST CLAIR R.W.: 'Estrogens and atherosclerosis: Phytoestrogens and selective estrogen receptor modulators.' CURRENT OPINION IN LIPIDOLOGY, (1998) 9/5 (457-463)., XP002126541

4). Priority (Box II)

If the priority is not valid, which could not be checked, further documents (D16, D17) cited in the International Search Report will become relevant.

5.) Invention 1

A composition comprising an ER $\beta$  ligand and its use as vasculoprotector; claims 1, 2, 4-26.

5.1). Novelty (Box V)

The beneficial effects of dietary soybean protein (which contains genistein) compared with animal proteins on plasma lipids, lipoproteins and atherosclerosis have been known for about 50 years according to D13. Thus D13 and also D1-D12 and D14, all relating to a composition containing genistein and its use in i.a. atherosclerosis, is novelty-destroying for claims 1, 2, 4-26 (Art. 33 (2) PCT). D8, D9 (page 197 col. 1 first paragraph) and D14 specifically relate to the use of

genistein for the treatment of postmenopausal females.

However, D1 apparently can only be taken into consideration if this document was publicly available before July 06, 1998 (or if the priority for the present application is not valid).

**5.2). Industrial Applicability (Box V)**

For the assessment of the present claims 9-19, 20 (partially) and 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**6). Invention 2**

A method for producing artificial tissues or organs including the step of treating the tissue with ER $\beta$  agonist and artificial tissues or organs obtained by said method (claims 27-29).

**6.1). Novelty (Box V)**

From the description page 7 lines 15-17 it seems to be known in the art how to produce blood vessels.

If the treatment of such vessels with genistein, which treatment is a process parameter, does not leave identifiable traces in the final product, the artificial tissue of claim 29 lacks novelty (Art. 33 (2) PCT).

The method of claims 27 and 28 appears to be novel, e.g. over D15.

**6.2). Inventive Step (Box V)**

Knowing about the beneficial effects of genistein from the prior art the skilled

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

---

International application No. PCT/GB99/02157

person has an incentive to try to genistein, to e.g. reduce intimal thickness, with a very high expectation of success in view of either D3, D6, D7, or D12.  
Hence claims 27-29 lack an inventive step (Art. 33 (3) PCT).

by fax and post

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:  
DEAN, John P.  
WITHERS & ROGERS  
Goldings House  
2 Hays Lane  
London SE1 2HW  
GRANDE BRETAGNE

Computer Log Date	11/10
Entered By	UW
Fee Earner	JPD

PCT

WRITTEN OPINION

(PCT Rule 66)

Fax no. 44 177 925 3570


Date of mailing  
(day/month/year) 05.10.2000Applicant's or agent's file reference  
KB123PCT**REPLY DUE** within 0 month(s) and 22 days  
from the above date of mailingInternational application No.  
PCT/GB99/02157International filing date (day/month/year)  
06/07/1999Priority date (day/month/year)  
06/07/1998International Patent Classification (IPC) or both national classification and IPC  
C07K14/00Applicant  
KARO BIO AB et al.

- This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
  - ☒ Basis of the opinion
  - ☒ Priority
  - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
  - ☒ Lack of unity of invention
  - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
  - ☐ Certain document cited
  - ☐ Certain defects in the international application
  - ☐ Certain observations on the international application

- The applicant is hereby **invited to reply** to this opinion.

**When?** See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).**How?** By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.**Also:** For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.**If no reply is filed**, the international preliminary examination report will be established on the basis of this opinion.

- The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 06/11/2000.

Name and mailing address of the international  
preliminary examining authority:

 European Patent Office  
D-80298 Munich

Authorized officer / Examiner

Heimann-Pohl, B

Formalities officer (incl. extension of time limits)



**I. Basis of the opinion**

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

**Description, pages:**

1-16 as originally filed

**Claims, No.:**

1-29 as originally filed

**Drawings, sheets:**

1/5-5/5 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

**II. Priority**

1. ☐ This opinion has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:
- ☐ copy of the earlier application whose priority has been claimed.
  - ☐ translation of the earlier application whose priority has been claimed.
2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this opinion, the international filing date indicated above is considered to be the

## 3. Additional observations, if necessary:

see separate sheet

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-2 (partially), 3, 4-29 partially,

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the said claims Nos. 1-19, 20 (partially), 21-29.

**IV. Lack of unity of invention**

1. In response to the invitation (Form PCT/IPEA/405) to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.
- ☒ paid additional fees.
- ☐ paid additional fees under protest.
- ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with for the following reasons and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees:

3. Consequently, the following parts of the international application were the subject of international preliminary

examination in establishing this opinion:

☒ all parts.

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

**1. Statement**

Novelty (N)	Claims	1, 2, 4-26, 29
Inventive step (IS)	Claims	27-29
Industrial applicability (IA)	Claims	

**2. Citations and explanations**

**see separate sheet**

**WRITTEN OPINION  
SEPARATE SHEET**

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International application No. PCT/GB99/02157

1). Non-unity (Box)

The International Preliminary Examination Authority (IPEA) agrees with the finding of the International Searching Authority (ISA) that the international application contains 2 inventions.

The problems to be solved by the present application are (1) to provide for a vasculoprotective composition and to provide for vasculoprotection and (2) to provide a method for producing artificial tissues or organs and artificial tissues or organs obtained by said method.

The proposed solution for (1) is to use ER $\beta$  ligands, e.g. genistein, as vasculoprotector and the proposed solution for (2) is to treat a tissue with an agonist of ER $\beta$  and thereby obtaining artificial tissues or organs.

The additional fee was paid, hence examination will be carried out for invention 1 and 2.

- 2). The unspecified antagonist of claim 3, the unspecified ligands and agonists of claims 1, 2, 4-19 and 21-29 (or the uses of these substances) and the chemical derivative or structural analogue of claim 20 were not searched since the lack of clarity was such that a meaningful complete search was impossible. Consequently, it is not possible to carry out a preliminary examination on matter which has not been searched. Search was restricted to genistein, thus all claims are examined with regard to genistein.



- MOLECULAR BIOLOGY, (1998) 65/1-6 (219-224).., XP002126532
- D3: TAKAMURA, HIROYUKI: 'Immunosuppressive effects of a tyrosine kinase specific inhibitors ( genistein ) on the rejection of rat allogeneic small bowel transplantation' KANAZAWA DAIGAKU JUZEN IGAKKAI ZASSHI (1995), 104(6), 719-731, XP002126533
- D4: BECKELER, KLAUS ET AL: 'Differential effects of immunosuppressive cyclosporine A and inhibitors of protein kinases on cytokine induced cell proliferation of umbilical cord artery smooth muscle cells: The role of endothelial supernatants on TNF-alpha effects.' EUROPEAN JOURNAL OF CELL BIOLOGY, (1996) VOL. 69, NO. SUPPL. 42, PP. 126. MEETING INFO.: 21ST ANNUAL MEETING OF THE GERMAN SOCIETY FOR CELL BIOLOGY HAMBURG, GERMANY MARCH 24-28, 1996, XP002126534
- D5: KUIPER ET AL.: 'Comparison of the ligand Binding Specificity and Transcript Distribution of Estrogen Receptors alpha and beta' ENDOCRINOLOGY, vol. 138, no. 3, 1997, pages 863-870, XP002126536 cited in the application
- D6: KAPIOTIS S ET AL: 'Genistein, the dietary-derived angiogenesis inhibitor, prevents LDL oxidation and protects endothelial cells from damage by atherogenic LDL.' ARTERIOSCLEROSIS, THROMBOSIS, AND VASCULAR BIOLOGY, (1997 NOV) 17 (11) 2868-74., XP002126537
- D7: BALARAM S.K. ET AL: 'Cell adhesion molecules and insulin-like growth factor-1 in vascular disease.' JOURNAL OF VASCULAR SURGERY, (1997) 25/5 (866-876).., XP002126538
- D8: HONORE E K ET AL: 'Soy isoflavones enhance coronary vascular reactivity in atherosclerotic female macaques.' FERTILITY AND STERILITY, (1997 JAN) 67 (1) 148-54., XP002126539
- D9: CLARKSON T.B. ET AL: 'The nonhuman primate model of the relationship between gonadal steroids and coronary heart disease.' PROGRESS IN CARDIOVASCULAR DISEASES, (1995) 38/3 (189-198).., XP002126540
- D10: US-A-5 919 813 (DE JUAN JR EUGENE) 6 July 1999 (1999-07-06)
- D11: DATABASE WPI Section Ch, Week 199826 Derwent Publications Ltd., London, GB; Class B02, AN 1998-292041 XP002126542 & JP 10 101561 A (SHIKOKU NOGYO SHIKENJO), 21 April 1998 (1998-04-21)
- D12: DATABASE WPI Section Ch, Week 199720 Derwent Publications Ltd., London, GB; Class A96, AN 1997-215838 XP002126543 & JP 09 056807 A

(KANEBUCHI KAGAKU KOGYO KK), 4 March 1997 (1997-03-04)

D13: M S ANTHONY ET AL: 'Soybean isoflavones improve cardiovascular risk factors without affecting the reproductive system of peripubertal rhesus monkeys' JOURNAL OF NUTRITION, XX, XX, vol. 126, no. 1, page 43-50 XP002095625 ISSN: 0022-3166

D14: WO 98 08503 A (NOVOGEN RES PTY LTD) 5 March 1998 (1998-03-05)

D15: WO 93 23090 A (SHERWOOD MEDICAL COMPANY) 25 November 1993 (1993-11-25)

D16: DATABASE WPI Section Ch, Week 199932 Derwent Publications Ltd., London, GB; Class B02, AN 1999-374524 XP002126544 & JP 11 139974 A (KUREHA CHEM IND CO LTD), 25 May 1999 (1999-05-25)

D17: ST CLAIR R.W.: 'Estrogens and atherosclerosis: Phytoestrogens and selective estrogen receptor modulators.' CURRENT OPINION IN LIPIDOLOGY, (1998) 9/5 (457-463)., XP002126541

4). Priority (Box II)

If the priority is not valid, which could not be checked, further documents (D16, D17) cited in the International Search Report will become relevant.

5.) Invention 1

A composition comprising an ER $\beta$  ligand and its use as vasculoprotector; claims 1, 2, 4-26.

5.1). Novelty (Box V)

The beneficial effects of dietary soybean protein (which contains genistein) compared with animal proteins on plasma lipids, lipoproteins and atherosclerosis have been known for about 50 years according to D13. Thus D13 and also D1-D12 and D14, all relating to a composition containing genistein and its use in i.a. atherosclerosis, is novelty-destroying for claims 1, 2, 4-26 (Art. 33 (2) PCT). D8, D9 (page 197 col. 1 first paragraph) and D14 specifically relate to the use of genistein for the treatment of postmenopausal females

However, D1 apparently can only be taken into consideration if this document was publicly available before July 06, 1998 (or if the priority for the present application is not valid).

**5.2). Industrial Applicability (Box V)**

For the assessment of the present claims 9-19, 20 (partially) and 21-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**6). Invention 2**

A method for producing artificial tissues or organs including the step of treating the tissue with ER $\beta$  agonist and artificial tissues or organs obtained by said method (claims 27-29).

**6.1). Novelty (Box V)**

From the description page 7 lines 15-17 it seems to be known in the art how to produce blood vessels.

If the treatment of such vessels with genistein, which treatment is a process parameter, does not leave identifiable traces in the final product, the artificial tissue of claim 29 lacks novelty (Art. 33 (2) PCT).

The method of claims 27 and 28 appears to be novel, e.g. over D15.

**6.2). Inventive Step (Box V)**

Knowing about the beneficial effects of genistein from the prior art the skilled person has an incentive to try to genistein, to e.g. reduce intimal thickness, with a

very high expectation of success in view of either D3, D6, D7, or D12.  
Hence claims 27-29 lack an inventive step (Art. 33 (3) PCT).

- 7). The applicant is requested to file amendments by way of replacement pages in the manner stipulated by Rule 66.8(a) PCT. In particular, fair copies of the amendments should be filed preferably in triplicate.

Moreover, the applicant's attention is drawn to the fact that, as a consequence of Rule 66.8(a) PCT the examiner is not permitted to carry out any amendments under the PCT procedure, however minor these may be.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 34(2)(b) PCT, the applicant is requested to clearly identify the amendments carried out, no matter whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see also Rule 66.8(a) PCT).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.

Any information the applicant may wish to submit concerning the subject-matter of the invention, for example further details of its advantages or of the problem it solves, and for which there is no basis in the application as filed, should be confined to the letter of reply and not be incorporated into the application (Article 34(2)(b) PCT).

- 8). In order to avoid any further delay the IPEA is prepared to discuss the case over the telephone. In case the applicant wishes to answer this written opinion by filing a response he is kindly requested to use the following Fax number:  
**+49 89 2399 7725** and to inform the Examiner before sending the Fax.



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Creation date: 10-31-2003  
Indexing Officer: TGE BRYESUS - TSIGEREDA GEBRYESUS  
Team: OIPEBackFileIndexing  
Dossier: 09719658

Legal Date: 01-09-2001

No.	Doccode	Number of pages
1	M905	2

Total number of pages: 2

Remarks:

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